Predictive and Prognostic Value of C-reactive Protein/Albumin and Neutrophil/Lymphocyte Ratio in the Patients Diagnosed with Acute Pancreatitis in Emergency Department

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SD, BB and UMK designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors BB, MD and SD managed the analyses of the study. Authors BC and BB managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aims: Acute pancreatitis is a severe inflammation of the pancreas presenting sudden onset with high morbidity and mortality. Simple, accessible, cost-efficient and feasible laboratory tests are still needed to demonstrate the prognosis of the patients. The aim of the present study was to search the efficiency of CRP/Alb ratio as a biochemical marker on mortality and clinical progress in the patients diagnosed with acute pancreatitis in correlation with APACHE-2.
Methodology: This prospective case-control study was conducted with the patients diagnosed with acute pancreatitis through Atlanta criteria and healthy volunteers as a control group in the emergency department. Demographic characteristics, vital signs, ultrasound reports, clinical outcomes, neutrophil, lymphocyte, neutrophil/lymphocyte ratio (NLR), CRP, albumin and CRP/Alb ratio, APACHE-2 score within control and patient groups were recorded. Logistic regression analysis was performed to distinguish healthy volunteers from acute pancreatitis cases.

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Results: There was a statistically significant difference between CRP/Albumin and NLR measurements according to the groups and we found that the measurements of the patient group were significantly higher than the control group. The cut-off point for CRP/Albumin and NLR was found to be respectively 1.08, 4.04 and above. (Respectively; sen: 76.64%, 78.50%; spe: 97.20%, 97.20%; PPV: 96.47%, 96.55%; NPV: 80.62%, 81.89%; the accuracy: 86.92%, 87.85%). APACHE-2 scores ranged from 0 to 16, with a mean of 5.80±3.92. The probability of acute pancreatitis was significantly higher in patients with high CRP/Albumin and NLR.
Conclusion: This study showed that CRP/Alb ratio and NLR were positively correlated with APACHE-2 scores that designed for prognosis in patients with acute pancreatitis.

1. INTRODUCTION

Acute pancreatitis (AP) is a severe inflammation of the pancreas presenting sudden onset and severe abdominal pain with high morbidity and mortality. Incidence is between 13 and 45 per 100,000 individuals. Although overall mortality is about 2% to 5%, such ratio may increase to 10% to 30% in severe acute pancreatitis [1]. Acute pancreatitis has a wide clinical manifestation range from self-limiting state to multiple organ failure and severe presentations accompanied by pancreatic necrosis. There are various biochemical tests, imaging methods, scoring systems to determine severity of the disease and need for intensive care. Some biochemical markers including C-reactive protein (CRP), amylase, lipase, trypsin and procalcitonin to diagnose the disease and detect the severity; however, there is not a consensus on diagnosis, prognosis and treatment assessment [2].

Various scoring methods were developed for early recognition of acute pancreatitis and treatment planning. The most common scoring methods are The Ranson criteria and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) 2. However, simple, accessible, cost-efficient and feasible laboratory tests are still needed to demonstrate the prognosis of the patients with acute pancreatitis in the emergency department referrals.

As is known, acute pancreatitis is increased inflammatory response of the pancreas gland [3]. C-reactive protein and albumin (Alb) are widely used inflammatory markers in the serum to predict the mortality in critical patients. Diagnostic roles of CRP and Alb may be explained by critical states reflecting the inflammatory process in acute phases. CRP is an acute phase protein which significantly increases in infection or inflammation. Serum albumin level is a reliable predictor which may be analyzed in the laboratory and recommended for critical patients with different diseases. Many studies showed a correlation between CRP/Alb ratio and diffuse organ dysfunction [3,4,5].

The aim of the present study was to search the efficiency of CRP/Alb ratio as a biochemical marker on mortality and clinical progress in the patients diagnosed with acute pancreatitis in the emergency department in correlation with APACHE-2.

2. MATERIALS AND METHODS

The study was conducted prospectively in the Department of Emergency Medicine of Kanuni Sultan Suleyman Training and Research Hospital within Health Sciences University between 01.10.2018–31.03.2019 with the approval of the ethics committee in patients with a pre-diagnosis of acute pancreatitis. Patients who were diagnosed with acute pancreatitis aged 18 years or older in our emergency department were included in the study. Patients diagnosed with AP according to Atlanta criteria were included in the study group and healthy volunteers were included in the control group. In this study, all patients with an additional diagnosis except acute pancreatitis, whose follow-up was discontinued, who did not give consent and all patients under 18 years of age were excluded from the study. Also the patients who have chronic diseases that may affect the metabolism of albumin and the value of CRP (malignancy/immunosuppression, cirrhosis, cardiac failure, malabsorption, chronic kidney failure), were excluded.

AP was diagnosed through Atlanta criteria which requires presence of at least 2 of the following: 1) abdominal pain which is highly suggestive of acute pancreatitis; 2) elevations in serum amylase and/or lipase to more than 3 times more than upper limit; 3) presence of characteristic radiological findings (ultrasound (USG) or computerized tomography (CT)) of AP (3).

Demographic characteristics, vital signs, ultrasound reports and clinical outcomes (exitus, admission, discharge) were recorded into the case form. Neutrophil, lymphocyte, neutrophil/lymphocyte ratio (NLR), CRP, albumin and CRP/Alb ratio values at referral were recorded. All patients had intravenous contrast whole abdominal computed tomography and reports were obtained. APACHE-2 scores were calculated and recorded.

2.1 Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, and percentage, minimum, maximum) were used to evaluate the study data. Conformity of quantitative data t normal distribution was tested through Shapiro-Wilk test and graphical analyses. Student t test was used to compare qualitative variables with normal distribution; comparison of non-normally distributed quantitative variables was performed through Mann Whitney U test. Spearman's correlation analysis was used to assess the associations between quantitative variables. Pearson's Chi-Square test was used to compare qualitative data. Significance was evaluated at least $p<0.05$.

A logistic regression analysis to define the patients diagnosed acute pancreatitis among two groups was conducted after the first analyses. Later logistic regression analyses with enter method showed that CRP/Alb and NLR were independent significant different parameters between groups. Thus, we analyzed area under the curve measures of CRP/Alb and NLR.

The power analysis was performed through G*Power (v3.1.9) program to determine the sample count. Study power is expressed as 1-β (β=type 2 error probability); and the studies usually should have a power by 80%. It was calculated that 84 individuals should be enrolled at least to demonstrate a correlation at 0.300 between APACHE-2 score and CRP/Alb ratio and existence with a power by 80%.

3. RESULTS

This study was performed with 107 of whom were case group and 107 were control group. 62.1% (n=133) of the cases were female and 37.9% (n=81) were male; The ages ranged from 18 to 95 years with a mean of 56.95±15.22 years.

Descriptive characteristics of the cases are shown in Table 1.

Table 1. Comparison of demographic and laboratory parameters among cases and controls

	Patient group (n=107)	Control group (n=107)	*p*	Mean Difference (%95 CI)
Age; *(Mean±Sd)*	57,06±19,21	56,85±9,60	[a]0,922	0,206
(%95 CI Mean)	(53; 61)	(55; 59)		(-3,905; 4,317)
CRP; *(Q1-Q3 (Median))*	4,6-45,6 (17)	1-3 (2)	[b]0,001**	34,482
(%95 CI Mean)	(26; 47,2)	(1,9; 2,4)		(23,853; 45,111
Albumin; *(Q1-Q3 (Median))*	3,8-4,4 (4,1)	4-4,4 (4,3)	[b]0,010*	-0,205
(%95 CI Mean)	(3,9; 4,1)	(4,2; 4,3)		(-0,317; -0,092)
CRP/Alb; *(Q1-Q3 (Median))*	1,1-12,6 (3,9)	0,2-0,7 (0,5)	[b]0,001**	9,190
(%95 CI Mean)	(6,8; 12,5)	(0,5; 0,6)		(6,331; 12,048)
Neutrophil; *(Q1-Q3 (Median))*	7,1-12,9 (9,5)	3,9-6 (4,8)	[b]0,001**	5,635
(%95 CI Mean)	(9,4; 11,8)	(4,7; 5,2)		(4,369; 6,875)
Lymphocyte; *(Q1-Q3 (Median))*	0,8-1,9 (1,3)	2-2,8 (2,4)	[b]0,001**	-0,860
(%95 CI Mean)	(1,3; 1,9)	(2,3; 2,6)		(-1,165; -0,554)
NLR; *(Q1-Q3 (Median))*	4,4-14,5 (7,1)	1,5-2,7 (2)	[b]0,001**	8,563
(%95 CI Mean)	(8,7; 12,8)	(2; 2,4)		(6,541; 10,586)
	n (%)	n (%)		
Gender Female	69 (64,5)	64 (59,8)	[c]0,481	-
Male	38 (35,5)	43 (40,2)		

Q1: First quarter; Q3: Third quarter
[a]*Student t Test;* [b]*Mann Whitney U Test;* [c]*Pearson Chi-Square Test*
**p<0,05; **p<0,01*

CRP measurements ranged from 0.2 to 336, with an average of 19.37±42.77; Albumin measurements ranged from 1.8 to 5.2, with an average of 4.14±0.43; CRP/Alb measurements ranged from 0.1 to 98.5, with an average of 5.10±11.48. Neutrophil measurements ranged from 1.4 to 56.3, with an average of 7.77±5.37; Lymphocyte measurements ranged from 0.2 to 12.3, with an average of 2.02±1.21; NLR measurements ranged from 0.3 to 58.9, with an average of 6.47±8.59. There was no statistically significant difference between age and sex distributions according to the groups (p> 0.05).

There was a statistically significant difference between the CRP measurements of the groups and the measurements of the patient group were higher than the control group (p=0.001; p<0.01). A statistically significant difference was found between albumin measurements according to the groups and the measurements of the patient group were lower than the control group (p=0.010; p<0.05). There was a statistically significant difference between CRP/Alb measurements and patient group measurements were higher than control group (p=0.001; p<0.01). There was a statistically significant difference between the neutrophil measurements compared to the groups and the measurements of the patient group were higher than the control group (p=0.001; p<0.01). Lymphocyte measurements were significantly different between the groups and the patient group measurements were lower than the control group

(p=0.001; p<0.01). Also, there was a statistically significant difference between NLR measurements and the patient group was higher than the control group (p=0.001; p<0.01) (Table 1).

In 51.4% (n=55) of the patient group, stone was observed by USG. APACHE-2 scores ranged from 0 to 16, with a mean of 5.80±3.92. When the last situation is examined; 70.1% (n=75) of the patients were hospitalized and 29.9% (n=32) were discharged (Table 2).

3.1 Determination of Cut off Point for CRP/Alb and NLR Measurements by Groups

There was a statistically significant difference between CRP/Alb and NLR measurements according to the groups and we found that the measurements of the patient group were significantly higher than the control group (Table 1). Based on this significance, it was considered to calculate the cut off point for CRP/Alb and NLR measurements. ROC analysis and diagnostic screening tests were used to determine cut off point according to the groups.

The cut-off point for CRP/Alb was found to be 1.08 and above. CRP/Alb for a cut-off value of 1.08; sensitivity 76.64%; specificity 97.20%; positive predictive value 96.47%; The negative predictive value is 80.62% and the accuracy

Table 2. Distributions of patient group characteristics

Patient Characteristics (n=107)		
Stone status by USG*; n (%)*		55 (51,4)
APACHE-2	*Min-Max (Median)*	0-16 (5)
	Mean±SD	5,80±3,92
Clinical outcome*; n (%)*	Hospitalization	75 (70,1)
	Discharged	32 (29,9)
	SD: Standard Deviation	

Table 3. Diagnostic screening tests and ROC curve results for CRP/Alb and NLR measurements by groups

	Diagnostic scan				ROC curve		*p*
	Cut off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% Confidence Interval	
CRP/ Alb	≥*1,08*	76,64	97,20	96,47	80,62	0,899	0,856-0,942	*0,001***
NLR	≥*4,04*	78,50	97,20	96,55	81,89	0,917	0,878-0,956	*0,001***
			***p<0,01*					

is 86.92%. The area under the ROC curve was 89.9% and the standard error was 2.2% (Table 3).

The risk of disease in cases with CRP/Alb measurements of 1.08 and above is 113,707 times higher (95% CI: 33,168-389,812) than cases with CRP/Alb measurements less than 1.08 (Fig. 1).

The cut off point for NLR was found to be 4.04 and above. NLR 4.04 for cutoff value; sensitivity 78.50%; specificity 97.20%; positive predictive value 96.55%; the negative predictive value is 81.89% and accuracy is 87.85%. The area under

the ROC curve was 91.7% and the standard error was 2.0% (Table 3).

Risk of disease in cases with NLR measurements 4.04 and above is 126,609 times higher (95% CI: 36,749-436,201) than in cases with NLR measurements less than 4.04 (Fig. 2).

While there was no statistically significant difference between age and sex distributions of patients with and without stones by USG (p>0.05); it was remarkable that the rate of women in the stone group was higher than the non stone group (p=0.067; p>0.05).
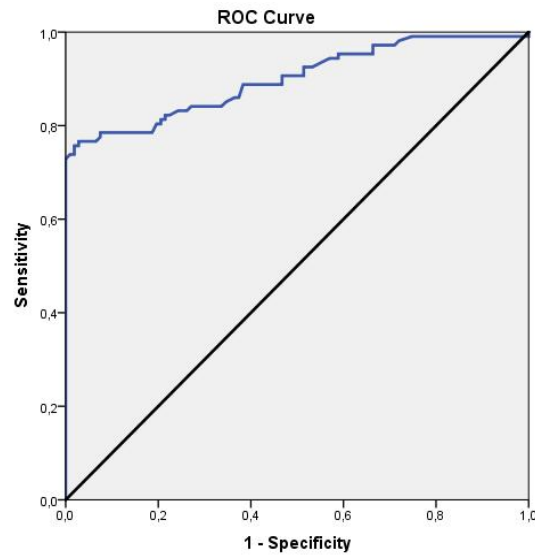
Fig. 1. ROC curve for CRP/Alb by groups
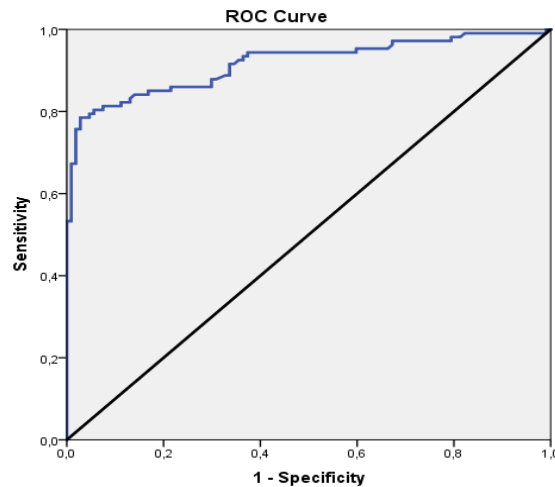
Fig. 2. ROC curve for NLR by groups

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CRP/Alb ratio and NLR measurements were not statistically different according to the presence of stones by USG (p>0.05). APACHE-2 scores did not show statistically significant differences according to the presence of stones by USG (p>0.05). In the stone detected by USG group, the rate of hospitalization was significantly lower than the non-stone group (p=0.006; p<0.01).

3.2 The Relationship between APACHE-2 - CRP/Alb Ratio

In the study group; a statistically significant correlation was found between APACHE-2 scores and CRP/Alb ratio (APACHE-2 increased as CRP/Alb Ratio increases) measurements at a level of 35.0% (r:0.350; p=0.001; p<0.01).

In the study group cases with stones detected by USG; There was no statistically significant relationship between APACHE-2 scores and CRP/Alb ratio measurements (r:0.195; p=0.154; p>0.05).

The cases without stones detected by USG; A statistically significant correlation was found between APACHE-2 scores and CRP/Alb ratio measurements at a level of 49.2% (r:0.492; p=0.001; p<0.01) (Fig. 3).

3.3 The Relationship between APACHE-2 and NLR

In the study group; A statistically significant correlation (APACHE-2 increased as NLR increases) was found between APACHE-2 scores and NLR measurements at 34.0% (r:0.340; p=0.001; p<0.01).

In the study group cases with stones detected by USG; A statistically significant correlation was found between APACHE-2 scores and NLR measurements at a level of 38.4% (r:0.384; p=0.004; p<0.01). The cases without stones detected by USG; A statistically significant weak correlation was found between APACHE-2 scores and NLR measurements at a level of 29.4% (r:0.294; p=0.034; p<0.05) (Fig. 4).

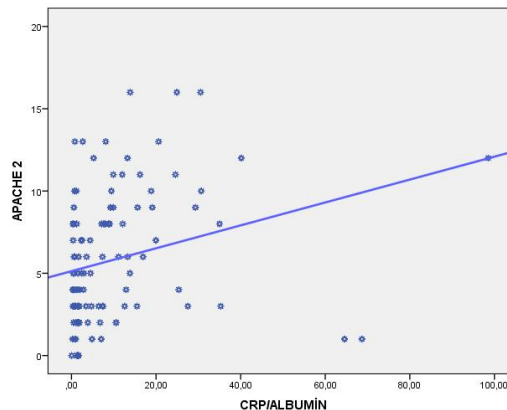**Fig. 3. Relationship between APACHE-2 scores and CRP/Alb ratio measurements**
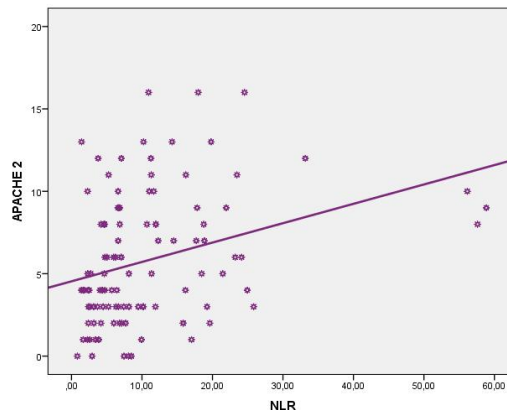

Fig. 4. Relationship between APACHE-2 scores and NLR measurements

4. DISCUSSION

Diagnosis of acute pancreatitis patients is based on amylase/lipase elevation, clinical findings and radiological imaging results. Numerous studies have been conducted on markers and scores that are thought to be used in the diagnosis and severity of the disease, and different sensitivity and specificity results have been obtained. Sensitivity and specificity ratios of scoring systems developed for acute severe pancreatitis patients vary between 55% and 90% depending on the scoring time and number of patients [6,7]. This situation increases the need for additional parameters to help clinicians use it. In our study, we found significantly higher sensitivity and specificity of CRP/Alb ratio and NLR values (sen: 76,64, spe: 97,20, sen: 78,50, spe: 97,20, respectively). The positive correlation between the severity of the disease and the inflammatory process is consistent with our results.

Amylase values of patients with acute pancreatitis can be found in the normal range in 19-32% of patients [8]. Therefore, in cases where amylase increases more than 3 times in the diagnosis of acute pancreatitis, specificity and sensitivity values are 95% and 61%, respectively [9]. Our study showed that CRP/Alb and NLR were significantly higher in acute pancreatitis at presentation than the control group. The specificity of cut-off values in patients with suspected acute pancreatitis was found to be significantly higher in both CRP/Alb and NLR. (97.2, the same in both). Park HS et al. reported that NLR values can be used to determine the severity of acute pancreatitis patients in the emergency department [10].

Although total white blood cell count is included in the Ranson criteria and APACHE-2 scores, it is not considered to be a useful marker for the diagnosis and prognosis of patients with pancreatitis alone. However, NLR is a predictor of prognostic and predictive value for inflammatory diseases and malignancies in many studies [11-13]. In our study, patients with NLR values above 4.04 had a significantly increased risk of acute pancreatitis compared to healthy volunteers. NLR elevation may be associated with increased neutrophils due to pancreatic tissue damage or delayed neutrophils and early lymphocyte apoptosis as a result of deterioration in cellular immunity [11,14]. In the literature, the cut-off values determined for the prediction of severe acute pancreatitis patients are 4.76 and

4.7 [11,15]. The cut off value of our study is similar to other studies.

In the literature, NLR has been associated with mortality in patients over 80 years of age who underwent emergency laparotomy [16,17]. High NLR values have been shown to be associated with increased long-term mortality and morbidity after major cardiac and vascular surgery and have been reported to be used in perioperative management and risk classification of these patients [18]. In a review by Stevens et al., survival was found to be associated with low inflammatory markers in patients with resectable pancreatic cancer [19]. Although there have been studies suggesting that NLR has a lower predictability to determine the severity of acute pancreatitis than scoring systems such as APACHE-2 and Ranson [20,21], no clear consensus has been reached yet. In our study, we found that NLR was positively correlated with APACHE-2, one of the mortality predictive scores for acute pancreatitis. In another study published in 2017; the increase in NLR has been shown to be associated with the severity of acute pancreatitis according to the Atlanta classification [15]. The results of our study are consistent with the literature.

In acute pancreatitis, it is known that mortality increases as the APACHE-2 score increases [22]. However, the Ranson criteria and APACHE-2 scoring systems used for prognosis and scoring are complex because they include 48 hours after the application and require many data [22]. CRP was found to be valuable especially in acute response because of its short half-life [23]. Many studies have shown that CRP is used in patients with acute pancreatitis during admission and treatment [3,24]. Kim et al. showed that CRP/Alb ratio is a predictor of mortality superior to CRP in patients with septic shock [4], in another study, it was reported that CRP/Alb ratio can be used as a prognostic factor in predicting mortality in sepsis and septic shock patients [25]. In the study conducted by Kaplan et al., CRP/Alb ratios of patients who died due to acute pancreatitis were found to be significantly higher, and their relationship with prognosis was emphasized [3]. In the same study, it was stated that CRP/Alb ratio was an independent variable for mortality. Again, Wang et al. reported that low albumin and high CRP are predictors of poor prognosis in patients with acute pancreatitis [26]. In our study, we found that CRP/Alb ratio was significantly higher in the study group compared to the control group and there was a significant

positive correlation between CRP/Alb ratio and NLR and APACHE-2 score in emergency applications. In the light of this information, the accuracy of the results of our study is supported.

5. CONCLUSION

This study showed that CRP/Alb ratio and NLR were positively correlated with scores designed for prognosis in patients with acute pancreatitis. We think that it can be used as repeatable, cheap and easily accessible for predicting prognosis in emergency departments. Further studies are needed to correlate these parameters with the scoring systems used.

6. LIMITATIONS

There are several limitations of our study. The first of these; Although our study was performed with sufficient number of patients after power analysis, the limitation of our study is the limited number of patients. Secondly, pancreatitis patient grouping could not be performed due to the small number of patients with severe pancreatitis. Evaluations for prognosis had to be made with an increase in APACHE-2 scoring, because we only got the values in admission and these tests were not repeated. The CRP level may also vary depending on the time period between the onset of the disease and the time to seek medical attention.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study is conducted prospectively in the Department of Emergency Medicine of Health Sciences University Kanuni Sultan Suleyman Training and Research Hospital between 01.10.2018–31.03.2019 with the approval of the ethics committee in patients with a pre-diagnosis of acute pancreatitis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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